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EXAMINER
STRZELECKA, TERESA E

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1637	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/890,297	VAN URK ET AL.	
	Examin r	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *54-113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-113* is/are rejected.

7)☒ Claim(s) *54,74,102* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 January 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group III in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicants cancelled previously pending claims 1-3, 8, 9, 20, 43-46 and 53, and added new claims 53-113, which will be examined in this office action.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on January 18, 2002 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Sequence Compliance Requirement

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN time of response to this office action WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R.. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

6. This application contains sequences without SEQ ID NOs in the specification (page 33, lines 3, 12, 21; page 34, lines 6 and 10; page 35, lines 15 and 16) and in the figures (Fig. 10-17).

Drawings

7. The drawings are objected to because In Figure 9, it is not clear which of the lines in the figure correspond to pH 4.0 and pH 7.0, since both lines are marked with the same open circles. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

8. Claims 54, 74 and 102 are objected to because of the following informalities: missing period at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 55, 57-60, 77, 80, 82-89, 91 and 112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 55 and 57-60 recite the limitation "the initial albumin solution" in line 1/2. There is insufficient antecedent basis for this limitation in the claim. Claim 54, from which all of these claims depend, contains a limitation "an albumin solution". It is also not clear whether "initial albumin solution" refers to albumin solution before purification or to "initial" purified albumin solution, obtained from one chromatographic step but before the next purification step.

B) Claim 77 recites the limitation "the initial albumin solution" in line 1/2. There is insufficient antecedent basis for this limitation in the claim. Claim 76, from which this claim depends, contains a limitation "an albumin solution". It is also not clear whether "initial albumin solution" refers to albumin solution before purification or to "initial" purified albumin solution, obtained from one chromatographic step but before the next purification step.

C) Claim 80 recites the limitation "the initial albumin solution" in line 1/2. There is insufficient antecedent basis for this limitation in the claim. Claim 79, from which this claim depends, contains a limitation "an albumin solution". It is also not clear whether "initial albumin solution" refers to albumin solution before purification or to "initial" purified albumin solution, obtained from one chromatographic step but before the next purification step.

D) Claims 82 and 84 are indefinite in claim 82, because claim 82 does do not recite a final process step which clearly relates back to the preamble. The preamble states that the method is for purifying an albumin solution, but the final process step is "collecting the albumin-containing anion-exchange flow through from step (xi)". Therefore, it is unclear as to whether the claim is intended to be limited to a method of albumin purification or a method of collecting a flow through from anion exchange step.

E) Claims 83 and 85 are indefinite in claim 83, because claim 83 does do not recite a final process step which clearly relates back to the preamble. The preamble states that the method is for

purifying an albumin solution, but the final process step is "eluting from the anion exchange matrix an anion exchange eluate". Therefore, it is unclear as to whether the claim is intended to be limited to a method of albumin purification or a method of eluting from anion exchange matrix anion exchange eluate.

F) Claims 86 and 88 are indefinite in claim 86, because claim 86 does do not recite a final process step which clearly relates back to the preamble. The preamble states that the method is for purifying an albumin solution, but the final process step is "collecting the albumin-containing cation-exchange flow through". Therefore, it is unclear as to whether the claim is intended to be limited to a method of albumin purification or a method of collecting a flow through from cation exchange step.

G) Claims 87 and 89 are indefinite in claim 87, because claim 87 does do not recite a final process step which clearly relates back to the preamble. The preamble states that the method is for purifying an albumin solution, but the final process step is "collecting the albumin-containing cation-exchange flow through". Therefore, it is unclear as to whether the claim is intended to be limited to a method of albumin purification or a method of collecting a flow through from cation exchange step.

H) Claim 91 recites the limitation "the initial albumin solution" in line 1/2. There is insufficient antecedent basis for this limitation in the claim. Claim 90, from which this claim depends, contains a limitation "an albumin solution". It is also not clear whether "initial albumin solution" refers to albumin solution before purification or to "initial" purified albumin solution, obtained from one chromatographic step but before the next purification step.

I) Claim 112 recites the limitation "the initial albumin solution" in line 1/2. There is insufficient antecedent basis for this limitation in the claim. Claim 111, from which this claim

depends, contains a limitation "an albumin solution". It is also not clear whether "initial albumin solution" refers to albumin solution before purification or to "initial" purified albumin solution, obtained from one chromatographic step but before the next purification step.

Claim Interpretation

11. Before proceeding with art rejections meaning of some of the terms present in the claims, for which the definitions were not provided by Applicants, will be interpreted. "Chromatography in the negative mode with respect to albumin" is interpreted to mean that albumin is adsorbed onto the chromatographic matrix, and "chromatography in the positive mode with respect to albumin" is interpreted to mean that albumin is not adsorbed onto the chromatographic matrix and is recovered in the flow-through. The term "initial albumin solution" is interpreted as the albumin solution before any of the purification steps. The term "glycoconjugate" is interpreted as any glycosylated material, such as glycoproteins, glycopeptides, etc.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. A note regarding rejection of the claims in which the order of steps was reversed: reversal of steps is considered to be prima facie obvious (see MPEP 2144.04 IV C), therefore claims in which the only difference is reversal of steps will be rejected together, for example, claims 54-75 and 90-110, claims 76-78 and 79-81, claims (82, 84) and (86, 88), claims (83, 85 and 87, 89).

MPEP 2144.04 IV

C. Changes in Sequence of Adding Ingredients

Ex parte Rubin , 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render prima facie obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.).

14. Claims 54, 56, 57, 59-67, 69, 70, 71, 74-76, 78, 79, 81, 90, 92, 93, 95-102, 104-106, 109-111 and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS), supported by Ohmura et al. (EP 0 570 916 A2; cited in the IDS) and Lindquist et al. (U.S. Patent No. 4,086,222; cited in the IDS).

A) Regarding claims 54, 76, 79, 90 and 111, Goodey et al. teach a process for purifying an albumin solution, the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the positive mode with respect to albumin in order to yield an albumin-containing CE product (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines1-10);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Goodey et al. teach a process comprising CE and AE chromatography, with a possible steps of affinity chromatography (AC), ultrafiltration and gel permeation chromatography before AE chromatography; see page 2, lines 6-31; page 3, lines 1-16);

(3) placing the albumin-containing AE product, without further purification, into a final container for therapeutic use (Goodey et al. teach placing the purified albumin into a plurality of

vials (page 6, lines 28-30) and placing the albumin solution into a bulk product formulation vessel, followed by completing formulation by addition of pharmacetutically acceptable excipients (page 27, lines 20-22).)

Regarding claims 56 and 92, Goodey et al. teach CE step utilizing a matrix such as SP-Sepharose FF, SP-Spherosil, CM-Spepharose FF, CM-Cellulose, Se-Cellulose or S-Spherodex (page 1, lines 30, 31; page 2, line 1; page 21, lines 5, 6). Goodey et al. do not specifically teach sulfopropyl subsituents as cation exchangers. As evidenced by Ohmura et al., SP stands for a sulfoprpyl group, for example, SP-Sephadex is sulfopropyl-dextran (page 5, lines 37-40). Since Goodey et al. teach SP-Sepharose FF and SP-Spherosil, they teach sulfoprpyl groups as cation exchangers.

Regarding claims 57 and 93, Goodey et al. teach initial albumin solution with a pH of 4.0-5.0 (page 3, lines 20, 21).

Regarding claims 59, 60 and 95, Goodey et al. teach initial albumin solution with octanoate concentration of 1-10 mM (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 61, 62, 78, 81, 96, 97, 109, 111 and 113, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 63 and 98, Goodey et al. teach AE step utilizing a matrix such as DEAE-Spherodex, Q-Hyper D, DEAE-cellulose, QAE-cellulose, TMAE, DMAE, DEAE Fractogel or DEAE Sepharose FF (page 25, lines 12-14). Goodey et al. do not specifically teach dialkylaminoalkyl subsituents as anion exchangers. As evidenced by Ohmura et al., DEAE means diethylaminoethyl group (page 6, lines 11-15), which is a species of dialkylaminoalkyl groups (Lindquist et al., col. 3, lines 53-56). Therefore, since Goodey et al. teach DEAE-Spherodex,

DEAE Fractogel or DEAE Sepharose FF, they teach dialkylaminoalkyl subsituents as anion exchangers.

Regarding claims 66 and 101, Goodey et al. teach that solution undergoing anion exchange chromatography has a conductivity of less than 4 mS/cm, namely, 2.5 $\pm$ 0.5 mS/cm (page 32, lines 1, 2).

Regarding claims 67 and 102, Goodey et al. teach AE step run in a positive mode with respect to albumin (page 25, lines 9-29).

Regarding claims 69 and 104, Goodey et al. teach ultrafiltration of albumin solution to a concentration between 20-120 g/L or 80-110 g/L before loading onto AE column (page 24, lines 20-24).

Regarding claims 70 and 105, Goodey et al. teach AE column equilibrated with a buffer with conductivity in the range of 1-4 mS/cm or 1.5-5 mS/cm (page 25, line 20; page 32, line 1).

Regarding claims 71 and 106, Goodey et al. teach elution of albumin from CE column with a solution of octanoate (page 31, lines 21-25), which has specific activity for albumin (page 2, lines 1-4). Goodey et al. do not teach elution of albumin from AE column using a solution of octanoate. However, they teach that pH of the eluting solution should be about 5.5, so that the binding of octanoate causes a significant overall charge difference (page 31, lines 23, 24). They also teach loading the eluate from the cation exchanger onto AE column equilibrated with a buffer of pH 5.5 (page 31, lines 27-29).

Regarding claim 74, Goodey et al. teach concentration of albumin prior to AE step (page 24, lines 20-24).

Regarding claims 75 and 110, Goodey et al. teach fermentation of yeast cells to produce recombinant albumin (page 10, lines 14-31; page 11-14; page 15, lines 1-9), primary separation of

albumin from other cell components (page 15, lines 23-31).

Regarding claims 76 and 79, Goodey et al. teach the albumin-containing AE (or CE) product being subjected to at least one step selected from the group consisting of buffer exchange; concentration; dilution; dialysis; diafiltration; pH-adjustment; treatment with a reducing agent; heating; cooling; and conditioning, before being placed into the final container (Goodey et al. teach concentration, diafiltration and formulation of purified albumin into a final product (page 26, lines 12-29; page 27).

B) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

C) Fisher et al. teach albumin purification using CE and AE chromatography in a negative mode with respect to albumin (Abstract; col. 2, lines 12-16).

Regarding claims 54, 76, 79, 90 and 111, Fisher et al. teach subjecting the albumin solution to cation exchange (CE) chromatography in the negative mode with respect to albumin in order to yield an albumin-containing CE product (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7).

Regarding claims 64 and 99, Fisher et al. teach AE step run in a negative mode with respect to albumin (col. 2, lines 30-38; col. 3, lines 46-56; col. 4, lines 1-7).

Regarding claims 65 and 100, Fisher et al. teach that albumin solution, which undergoes AE chromatography has a pH of 5.1-5.5 (col. 2, line 32).

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin of Fisher et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Fisher et al.,

would have been that using ion exchange in negative mode with respect to albumin maintained albumin in solution, and resulted in efficient albumin purification while minimizing potential alterations to albumin structure (col. 2, lines 4-17). The teaching of Fisher et al. regarding the anion exchange purification therefore enhances the ability of Goodey et al. to obtain highly purified albumin therapeutic treatments (Goodey et al., page 1, lines 1-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have eluted albumin from AE column with a buffer containing a compound having a specific affinity for albumin. The motivation to do so would have been that albumin elution could be accomplished with more specificity and efficiency, since no other proteins bound to a compound with specific affinity for albumin.

15. Claims 55, 77, 80, 82, 84, 86, 88, 91 and 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS), and further in view Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984).

A) Claim 55 is drawn to a process according to claim 54 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 77 is drawn to a process according to claim 76 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 80 is drawn to a process according to claim 79 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 91 is drawn to a process according to claim 90 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 112 is drawn to a process according to claim 111 wherein the initial albumin solution

contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step.

B) Neither Goodey et al. nor Fisher et al. teach initial albumin solution containing glycosylated albumin and the glycosylated albumin being bound during the cation exchange step.

C) Shaklai et al. teach that 10% of albumin present in human plasma is glycosylated (Abstract). Glycosylated albumin has altered ligand binding properties: bilirubin binding is lower by 50% and fatty-acid binding is reduced 20-fold (Abstract; Fig. 4, Fig. 5, page 3814, the last paragraph; page 3815). Shaklai et al. teach binding of glycosylated albumin peptides to cation exchange column (page 3813, third paragraph; Fig. 1).

D) Regarding claims 82 and 86, Goodey et al. teaches a process for purifying an albumin solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column

containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20).

Regarding claims 84 and 88, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

E) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

F) Fisher et al. teach albumin purification using CE and AE chromatography in a negative mode with respect to albumin (Abstract; col. 2, lines 12-16). Fisher et al. teach that the order of ion exchange steps is not critical (col. 2, lines 38-40).

Regarding claims 82 and 86, Fisher et al. teach a process for albumin purification (Abstract), the process comprising:

Regarding claims 82 and 86, Fisher et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with respect to albumin (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7);

(x) collecting the albumin-containing CE flow through (Fisher et al. teach collecting the fluid containing albumin after CE chromatography; col. 3, lines 64-66);

(xi) subjecting the albumin solution to AE chromatography in the negative mode with

respect to albumin (Fisher et al. teach contacting the albumin solution to be purified with an AE exchange matrix to remove proteins having isoelectric points above that of albumin (col. 2, lines 23-30; col. 3, lines 46-56; col. 4, lines 1-7);

(xii) collecting the albumin-containing AE flow through (Fisher et al. teach collecting the fluid containing albumin after AE chromatography; col. 3, lines 54-56).

G) Neither Goodey et al. nor Fisher et al. teach affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates.

H) Regarding claims 82 and 86, Shaklai et al. teach that 10% of albumin present in human plasma is glycosylated (Abstract). Glycosylated albumin has altered ligand binding properties: bilirubin binding is lower by 50% andfatty-acid binding is reduced 20-fold (Abstract; Fig. 4, Fig. 5, page 3814, the last paragraph; page 3815). Shaklai et al. teach separation of glycosylated albumin (= glycoconjugate) from non-glycosylated albumin on a GlycoGel B affinity column, to which glycosylated albumin bound, and non-glycosylated albumin was collected in a flow through (page 3812, seventh paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin of Fisher et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Fisher et al., would have been that using ion exchange in negative mode with respect to albumin maintained albumin in solution, and resulted in efficient albumin purification while minimizing potential alterations to albumin structure (col. 2, lines 4-17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed glycosylated albumin by affinity chromatography of Shaklai et al. in the method of albumin purification by Goodey et al. and Fisher et al. The motivation to do so, provided

by Shaklai et al., would have been that glycosylated albumin had impaired function of binding and transporting of fatty acids (Abstract; page 3816, the last paragraph) and that albumin glycosylation may contribute to long term diabetic complications (page 3812, second paragraph). Therefore, removing glycosylated albumin from albumin solution according to Shaklai et al. enhances the ability of Goodey et al. and Fisher et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25), without a danger of introducing into a patient an inactive protein which might also contribute to diabetic complications.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed glycosylated albumin by CE chromatography of Shaklai et al. in the method of albumin purification by Goodey et al. and Fisher et al. The motivation to do so, provided by Shaklai et al., would have been that glycosylated albumin had impaired function of binding and transporting of fatty acids (Abstract; page 3816, the last paragraph) and that albumin glycosylation may contribute to long term diabetic complications (page 3812, second paragraph). Therefore, removing glycosylated albumin from albumin solution according to Shaklai et al. enhances the ability of Goodey et al. and Fisher et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25), without a danger of introducing into a patient an inactive protein which might also contribute to diabetic complications.

16. Claims 58 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS) as applied to claims 54 and 90 above, and further in view of Curling ("Methods of Plasma Protein Fractionation", pp. 77-91, 1980; cited in the IDS).

A) Claim 58 is drawn to the method of claim 54 wherein the initial albumin solution has an albumin concentration of 10-250 g/L, and claim 94 is drawn to the method of claim 90 wherein the

initial albumin solution has an albumin concentration of 10-250 g/L.

B) Neither Goodey et al. nor Fisher et al. teach initial albumin solution has an albumin concentration of 10-250 g/L. Goodey et al. teach obtaining albumin from large-scale fermentation, with a fermenter the size of 4000 L (page 13, lines 20-23). They also teach that the expected yield of albumin is greater than 1.5 g/L of culture. Therefore, the total amount of albumin obtained from 4000 L would be at least 6000 g of albumin. They also teach that after pretreatment and centrifugation 75% of the albumin present id diluted culture is recovered, which would translate into at least 4500 g of albumin in a solution of unspecified volume, to be loaded onto an ion exchange column.

C) Curling teaches industrial scale purification of albumin on AE and CE columns, with 500 g of albumin in 16 L (about 31 g/L albumin) loaded onto the columns (Fig. 2, page 81, paragraphs 3-6; Table 1).

It would have been prima facie obvious to one of ordinary skill in the art to have used initial albumin concentrations of Curling (greater than 10 g/L) in the combined method of Goodey et al. and Fisher et al. The motivation to do so, provided by Curling, would have been that purification with this albumin concentration resulted in a 97% pure product (page 82, second paragraph).

17. Claims 68, 73, 103 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS) as applied to claims 54, 67, 90 and 102 above, and further in view of Ohmura et al. (EP 0 570 916 A2; cited in the IDS) and Chang (EP 0 422 769 A1; cited in the IDS).

A) Claim 68 is drawn to a process according to claim 67 wherein the albumin solution which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 73 is drawn to the process according to claim 67 wherein the albumin is eluted in the anion exchange

step with a buffer of pH 6.0-8.0. Claim 103 is drawn to a process according to claim 102 wherein the albumin solution which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 108 is drawn to the process according to claim 102 wherein the albumin is eluted in the anion exchange step with a buffer of pH 6.0-8.0.

B) Neither Goodey et al. nor Fisher et al. teach albumin solution which undergoes positive mode anion exchange chromatography with a pH of 6.0-8.0, or the albumin being eluted in the anion exchange step with a buffer of pH 6.0-8.0.

C) Ohmura et al. teach purification of albumin comprising AE chromatography step run in a positive mode with respect to albumin (page 6, lines 21-24). They teach that albumin can be adsorbed onto AE column using a phosphate buffer of pH 6 to 8, and eluted from the column using buffer with the same pH range (page 6, lines 18-24). Chang teaches albumin purification comprising a step of AE chromatography (Abstract). Chang teaches that at pH > 6.1 albumin becomes more readily bound to the anion exchange column (page 4, lines 31-33).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used a buffer with a pH of 6.0-8.0 of Ohmura et al. in the combined albumin purification method of Goodey et al. and Fisher et al. The motivation to do so, provided by Chang, would have been that at pH > 6.1 albumin bound better to AE column than contaminating proteins (page 4, lines 31-33).

18. Claims 72 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS) as applied to claims 54, 67, 71, 90, 102 and 106 above, and further in view of Ohmura et al. (EP 0 570 916 A2; cited in the IDS) and Chang (EP 0 422 769 A1; cited in the IDS).

A) Claim 72 is drawn to a process of claim 71 wherein the buffer comprises 20-90 mM

phosphoric acid salt, and claim 107 is drawn to a process of claim 106 wherein the buffer comprises 20-90 mM phosphoric acid salt.

B) Goodey et al. do not teach albumin elution buffer comprising 20-90 mM phosphoric acid salt. Fisher et al. teach a suitable eluent for a material absorbed on AE column being 0.1 M sodium phosphate (col. 4, lines 28-30).

C) Ohmura et al. teach purification of albumin comprising AE chromatography step run in a positive mode with respect to albumin (page 6, lines 21-24). They teach that albumin can be adsorbed onto AE column using a phosphate buffer of pH 6 to 8 and salt concentration of 0.001-0.05 M, and eluted from the column using buffer with the same pH range and salt concentration of 0.05 to 1 M (page 6, lines 18-24). They teach anion exchange column buffer of 50 mM phosphate (page 11, lines 49-51). Chang teaches albumin purification comprising a step of AE chromatography (Abstract). Chang teaches that at pH > 6.1 albumin becomes more readily bound to the anion exchange column (page 4, lines 31-33).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used a buffer with a pH of 6.0-8.0 of Ohmura et al. in the combined albumin purification method of Goodey et al. and Fisher et al. The motivation to do so, provided by Chang, would have been that at pH > 6.1 albumin bound better to AE column than contaminating proteins (page 4, lines 31-33).

19. Claims 83, 85, 87 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984), and further in view of Chang (EP 0 422 769 A1; cited in the IDS).

A) Regarding claims 83 and 87, Goodey et al. teaches a process for purifying an albumin

solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20).

Regarding steps (xi) and (xii) of claim 83 (or steps (ix) and (x) of claim 87), these are repeated steps (iii) and (iv). Goodey et al. do not specifically teach repeating AE step in a positive mode with respect to albumin.

Regarding claims 85 and 89, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

B) Goodey et al. do not teach albumin purification using CE chromatography run in a negative mode with respect to albumin.

C) Fisher et al. teach albumin purification using CE chromatography in a negative mode with respect to albumin (Abstract; col. 2, lines 12-16). Fisher et al. teach that the order of ion exchange steps is not critical (col. 2, lines 38-40).

Regarding claims 83 and 87, Fisher et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with respect to albumin (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7);

(x) collecting the albumin-containing CE flow through (Fisher et al. teach collecting the fluid containing albumin after CE chromatography; col. 3, lines 64-66);

D) Neither Goodey et al. nor Fisher et al. teach repeating AE chromoatography steps or affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates .

E) Regarding claims 83 and 87, Chang teaches repeating AE chromatography steps to remove contaminating proteins from albumin solution (Abstract; page 4, lines 17-39).

F) Shaklai et al. teach that 10% of albumin present in human plasma is glycosylated (Abstract). Glycosylated albumin has altered ligand binding properties: bilirubin binding is lower by 50% andfatty-acid binding is reduced 20-fold (Abstract; Fig. 4, Fig. 5, page 3814, the last paragraph; page 3815). Shaklai et al. teach separation of glycosylated albumin (= glycoconjugate) from non-glycosylated albumin on a GlycoGel B affinity column, to which glycosylated albumin

bound, and non-glycosylated albumin was collected in a flow through (page 3812, seventh paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE chromatography step run in a negative mode with respect to albumin of Fisher et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Fisher et al., would have been that using ion exchange in negative mode with respect to albumin maintained albumin in solution, and resulted in efficient albumin purification while minimizing potential alterations to albumin structure (col. 2, lines 4-17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed glycosylated albumin by affinity chromatography of Shaklai et al. in the method of albumin purification by Goodey et al. and Fisher et al. The motivation to do so, provided by Shaklai et al., would have been that glycosylated albumin had impaired function of binding and transporting of fatty acids (Abstract; page 3816, the last paragraph) and that albumin glycosylation may contribute to long term diabetic complications (page 3812, second paragraph). Therefore, removing glycosylated albumin from albumin solution according to Shaklai et al. enhances the ability of Goodey et al. and Fisher et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25), without a danger of introducing into a patient an inactive protein which might also contribute to diabetic complications.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have repeated the AE steps in the albumin purification method of Goodey et al., Fisher et al. and Shaklai et al. according to Chang. The motivation to do so, provided by Chang, would have been that repeating AE steps resulted in albumin purity of greater than 99% (page 4, lines 44-46).

20. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

TS
September 3, 2003 TS